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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte WILLIAM S. BRUSILOW

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Appeal 2011-001751
Application 10/758,415
Technology Center 1600

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Before ERIC GRIMES, JEFFREY N. FREDMAN, and
STEPHEN WALSH, Administrative Patent Judges.

FREDMAN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method for treating a polyglutamine disease. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

Background

"There are a number of neurodegenerative polyglutamine diseases, for example Huntington's disease . . . which are characterized by expanded genomic CAG sequences resulting in the synthesis and accumulation of polyglutamine tracts in brain proteins of unknown function" (Spec. 1, ll. 16-

20). The Specification teaches "a treatment for polyglutamine disorders caused by expanded genomic CAG nucleotides by reducing the availability of free glutamine in astrocytes . . . by the administration of effective amounts of L-methionine S-sulfoximine, L-ethionine S-sulfoximine, glufosinate and/or branched chain α-keto acids" (Spec. 7, ll. 4-12).

The Claims

Claims 1-5, 10, 11, and 21 are on appeal.[1] Claim 1 is representative. Claim 1 reads as follows:

> 1. A method for treating a polyglutamine disease, comprising administering a compound selected from the group consisting of L-methionine S-sulfoximine, L-ethionine S- sulfoximine, glufosinate and branched chain α-keto acids derived from leucine, isoleucine or valine, to a patient in need of such treatment.

The issue

The Examiner rejected claims 1-5, 10, 11, and 21 under 35 U.S.C. § 103(a) as obvious over Apostolakis,[2] Ginefri-Gayet,[3] Liedtke,[4] and Feurerstein[5] (Ans. 3-5).

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[1] Claims 6-9 and 12-20 are withdrawn (see App. Br. 2).
[2] Apostolakis et al., Long-Term Effects of the Administration of the Convulsive Substance DL-Methionine-DL-Sulfoximine to the Rabbit, 23 BRAIN RESEARCH BULLETIN 257-262 (1989).
[3] Ginefri-Gayet et al., Possible Link Between Brain Serotonin Metabolism and Methionine Sulfoximine-Induced Hypothermia and Associated Behavior in the Rat, 43 PHARMACOLOGY BIOCHEMISTRY BEHAVIOR 173-179 (1992).
[4] Liedtke et al., US 2003/0013650 A1, published Jan. 16, 2003.
[5] Feurerstein et al., US 2002/0173537 A1, published Nov. 21, 2002.

The Examiner finds that "Apostolakis teaches methionine sulfoximine (MSO) is a centrally acting neurotoxin with convulsive properties; it has been used in study of epilepsy. MSO suppresses the formation of glutamine" (Ans. 3). The Examiner finds that "Ginefri-Gayet teaches pharmaceutical unit doses in an amount of methionine sulfoxim[in]e of 50-75 micro gram/10 micro liters" (id.). The Examiner finds that "Liedtke teaches that the present invention relates to the identification in vertebrate animals including humans, of an ion channel for rapid conduction of cations" (id.). The Examiner finds that "Feurerstein et al. teach of a compound treating neurodegenerative diseases including polyglutamine diseases (see page 1, paragraph 0003). The composition is useful for treating a polyglutamine disease e.g. Huntington's disease" (id. at 4).

The Examiner finds that "[c]learly, the skilled artisan is provided with ample instruction and motivation to use MSO in the treatment of neurodegenerative diseases including polyglutamine diseases" (id. at 4-5).

Appellant contends that "though Apostolakis indicates that MSO suppresses the formation of glutamine and glutamate, Apostolakis also discloses that MSO is a centrally acting neurotoxin with convulsive properties" (App. Br. 6). Appellant contends that "Apostolakis uses MSO to induce seizures in order to investigate 'a possible correlation of the probability of occurrence of a seizure with the power spectrum characteristics of the interictal EEG in the rabbit' (page 257, left column)" (id.). Appellant contends that "Apostolakis concludes that administration of MSO to rabbits in addition to the known convulsive effects may also be responsible for hind leg myopathy. Therefore, Apostolakis explicitly teaches

away from using MSO as a therapeutic treatment for any diseases" (App. Br. 7).

Appellant contends that "Feurerstein is directed to a method for treating a polyglutamine disorder using 2- pyrrolidinone derivatives. Feurerstein does not teach the use of MSO and thus does not cure the deficiencies in Apostolakis, Ginefri-Gayet and Liedtke as discussed above" (id. at 9).

The issue with respect to this rejection is: Does the evidence of record support the Examiner's conclusion that the combination of Apostolakis, Ginefri-Gayet, Liedtke, and Feurerstein renders obvious the treatment method of claim 1?

Findings of Fact

The following findings of fact ("FF") are supported by a preponderance of the evidence of record.

1. Feurerstein teaches that "Huntington's disease (HD) is also associated with extracellular glutamate levels. . . . [I]t is caused by a CAG repeat expansion, corresponding to an elongated polyglutamine segment on the protein level" (Feurerstein, col. 1 ¶ 0003).

2. Feurerstein teaches that "[s]ubstances which prevent the excitotoxicity of and the plastic changes due to Glu by reducing the extracellular Glu level would be a crucial advantage for the therapy and prophylaxis of the pathological states" (Feurerstein, col. 1 ¶ 0004).

3. Apostolakis teaches that "METHIONINE sulfoximine (MSO) is a centrally acting neurotoxin with convulsive properties; it has been used

for a long time as a tool for the experimental study of epilepsy" (Apostolakis 257, col. 1).

4. Apostolakis teaches that "MSO suppresses the formation of glutamine and glutamate and it has been claimed to reduce the releasable pool of glutamate, aspartate and GABA" (Apostolakis 257, col. 1).

5. Apostolakis teaches that "[f]ollowing the IV MSO administration the animals became hyperactive and exhibited increased hind leg muscle tonus at 2 hr; at 4-5 hr tetanus-like seizures started" (Apostolakis 259, col. 1).

6. Apostolakis teaches that the "seizures were suppressed by high doses of diazepam . . . Two out of the 14 animals included in our observations . . . recovered fully by the 4th day, while the condition of the rest deteriorated further and finally lower limb rigid paralysis set in" (Apostolakis 259, col. 1-2).

7. Apostolakis teaches that "administration of small doses of MSO to rabbits, except for their already known convulsive effects, may also be responsible for hind leg myopathy" (Apostolakis 260, col. 2 to 261, col. 1).

8. Ginefri-Gayet teaches that the "convulsant molecule L-methionine-D,L-sulfoximine (MSO) intraperitoneally or intracerebroventricularly administered induced a decrease of body temperature in the restrained rat" (Ginefri-Gayet 173, col. 1).

9. Ginefri-Gayet teaches that "MSO administered at a convulsant dose elicited a time-dependent regional perturbation of 5-HT metabolism in the rodent brain" (Ginefri-Gayet 177, col. 1).

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10. Liedtke teaches an ion channel which "demonstrates activity as an osmoreceptor, and also demonstrates a role in mechanical stimulation and responsiveness" (Liedtke 1 0002).

Principles of Law

"'[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007).

> A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.

In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994).

Analysis

Feurerstein teaches treatment of Huntington's disease using substances which reduce extracellular Glutamate levels (FF 1-2), Feurerstein provides no teaching or suggestion of the specific compounds of claim 1.

Apostolakis and Ginefri-Gayet teach the use of methionine sulfoximine (MSO), and Apostolakis teaches that MSO reduces the releasable pool of glutamate (FF 3-9).

The Examiner does not identify, and we do not find, any reason other than the common ability to reduce extracellular glutamate levels, which links these references together.

We agree with Appellant that Apostolakis and Ginefri-Gayet teach away from the claimed invention (see App. Br. 6). There is no suggestion in Apostolakis or Ginefri-Gayet to use MSO in any sort of beneficial treatment whatsoever. There are express teachings in Apostolakis that MSO is a neurotoxin which induces epilepsy (FF 3), hyperactivity and tetanus like seizures (FF 5), and hind leg myopathy (FF 7). Ginefri-Gayet teaches that MSO causes hypothermia (FF 8) and convulsions (FF9).

While side effects alone would not necessarily represent a teaching away, the instant references teach nothing but negative effects of the administration of MSO (FF 3-9). There is no reference which teaches or suggests that MSO would have any positive therapeutic effect whatsoever.

We find the Examiner's argument that "if MSO administration causes undesired side effects, it will necessarily cause the same undesired effects in Appellant's treatment of poly glutamine disease" particularly unpersuasive. This argument confuses the issues. The issue is not whether MSO will inherently result in particular side effects, a result which is likely to be dose dependent. The issue is whether in light of references which teach only side effects and which do not suggest any therapeutic use for MSO, would the ordinary artisan have had any reason to apply MSO to a therapeutic use? Clearly, we find that no prima facie case of obviousness has been established.

The Examiner also mischaracterizes Apostolakis, when stating that "the prior art teaches that at lower concentration there has been some benefit of using MSO" (Ans. 7). Apostolakis treated 14 animals, with no previously identified disease, with MSO (see Apostolakis 257, col. 1-2). The 2 animals which recovered after MSO treatment were subjected to seizures and were simply shown to have recovered from the negative effects of the MSO treatment, not to have received any positive or therapeutic effect (see Apostolakis 259, col. 1-2). We do not consider treatment of healthy animals with a neurotoxin to constitute a benefit to those animals, even to those which recover.

Conclusion of Law

The evidence of record does not support the Examiner's conclusion that the combination of Apostolakis, Ginefri-Gayet, Liedtke, and Feurerstein renders obvious the treatment method of claim 1.

## SUMMARY

In summary, we reverse the rejection of claims 1-5, 10, 11, and 21 under 35 U.S.C. § 103(a) as obvious over Apostolakis, Ginefri-Gayet, Liedtke, and Feurerstein.

## REVERSED

JNF

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